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10/019,387	03/26/2003	Maurizio Dalle Carbonare	0259-0411PUS1	6340

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EXAMINER	
MAEWALL, SNIGDHA	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/08/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/019,387	DALLE CARBONARE ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-5,13,14,17-19 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5,13,14,17-19 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. Receipt of Applicant's Arguments/Remarks and Amendments filed on 09/24/10 is acknowledged.

Claims 1-2, 6-12, 15-16 and 20-21 have been canceled in this Application.

Claims 3-4, 14, 17-18 and 22 have been amended.

New claims 23-25 have been added.

Accordingly, claims **3-5, 13-14, 17-19 and 22-25** are pending in this application.

The rejections made in the previous office action have been withdrawn in view of applicant's amendments to claims.

Applicant's amendments to the claims necessitated the following new rejections.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims **3-5, 13-14, 17-19 and 22-25** are rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (Clinical materials (1991, presented in IDS) in view of Valentini et al. (US USP 5,939,323) and further in view of Dorigatti et al. (USP 5,824,335) and optionally in view of Della Valle et al. (USP, 5,676,964).

Davidson et al. teaches hyaluronate derivatives and their application to wound healing and wound repair with reduced **scarring** (see title and page 171, second column). The reference teaches that hyaluronic acid and its derivatives show as biomaterial in wound healing applications. The hyaluronate treated wounds tended to accumulate collagen more slowly hence showing the capacity of such biomaterials in modifying the scarring process. Such ability shows effect in improving wound healing and repair process (see the first page). The reference teaches formulations can be fabricated into gels and films (reads on non woven materials as also defined in instant specification (see page 172, 1-5 lines). Experimental procedures have been shown on page 172, on both columns. The results show that ability of hyaluronate and its esterified derivatives stimulate early organization of wound site while moderating the excessive accumulation of collagen at the stage of scar formation. (See page 174 columns 2, last paragraph).

Davidson et al. do not specifically teach benzyl esters as claimed and utilization of additional biological compound.

Valentini teaches a scaffold made up of hyaluronic acid derivative for use of wound healing, tissue repair and tissue reconstruction which comprises a biologically active molecule, abstract. The reference teaches use of HYAFF 11 which is benzylester of hyaluronic acid and 75% benzyl ester of hyaluronic acid such as taught in column 9, lines 39-40. Growth factors were introduced with gel materials, see column 10 e section.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use 75% benzyl hyaluronic acid esters for the treatment of scarring on the skin by using the composition provided by Valentini et al. motivated by the teachings of Davidson et al. which teaches utilization of hyaluronate esters in wound healing and scarring treatment. Since the instant specification provides experimentation of scarring treatment after creating wound in an animal and then observing the scarring effect, it is evident that wound healing ester of hyaluronic acid of Valentini would treat scarring as per Davidson et al absent evidence to contrary. Regarding claim 19, patent office is not equipped with laboratory to conduct experiments; since the prior art teaches the claimed components and claimed method of treating, one of ordinary would expect similar results. A skilled artisan would have been motivated to use derivatives of hyaluronic acid such as esters of hyaluronic acid in treating the scarring of the skin and treatment of wound with a reasonable expectation of success.

The references discussed above do not teach non-woven fabric for application. Dorigatti et al. teach application biodegradable, biocompatible and bioabsorbable non-woven fabric materials for use in surgery for regeneration of tissues, the fabric provides better absorption and can be better moulded for the surface to be covered and absorbs

liquids such as solutions of disinfectants etc. the non woven fabric includes esters of hyaluronic acid, see abstract, column 2, lines 5-10 and 20-25.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use non woven fabric in the teachings of Davidson and Valentini for better absorption properties and flexibility motivated by the teachings of Della Valle et al.

The references discussed above do not disclose that 25% of carboxyl group of benzyl ester is free or salified. Since Valentini discloses 75% benzyl ester, it is apparent that rest of the carboxyl groups will be free.

To that end, DellaValle et al. teach process of hyaluronic acid esterification in which the extent of esterification can be varied and which shows that esterification can be from 25% to 75% and rest of the carboxyl groups are either free or salified, the reference also teaches salifiaction with inorganic salt, ,alkaline, potassium salt, see claims.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have salify the free carboxyl groups of hyaluronic acid ester because the process was known in the art. Utilization of known process of esterification would have resulted predictable results. Application of fabric to obtain optimum results for wound healing is optimizable parameter depending upon the extent of treatment required.

4. Claims **3-5, 13-14, 17-19 and 22-25** are rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (Clinical materials (1991, presented in IDS) in view of Dorigatti et al. (WO 94/17837, presented in IDS) and further in view of in view of Dorigatti et al. (USP 5,824,335) and optionally in view of Della Valle et al. (USP, 5,676,964).

The teachings of Davidson have been discussed above, the reference of Davidson does not teach benzyl ester specifically and utilization of additional biologically or pharmacologically active compound.

Dorigatti (WO) teaches multilayer non woven material comprising a layer in contact with the skin comprising esters of hyaluronic acid; the material can be utilized in medical applications including surgery, abstract. By using non woven tissue production techniques, it is possible to obtain procedures which combine flexibility with the capacity to absorb fluids, see page 1, lines 19-23. The non woven materials can be used in dermatology and treating skin pathologies, see page 3, and lines 22-23. The hyaluronic esters used can be those described in EPA 0216453, USP 4,851,521, 4,965,353 and 5202431, used alone or in mixtures in varying amount percentages, see page 4, lines 27-29. The layer can also comprise collagen, polysaccharides in the form of gel, agar etc. (Reads on biological or pharmacological compound) the example 1 on page 7 discloses HYAFF 11 and non woven layer, the reference also teaches 75% benzyl ester.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use 75% benzyl hyaluronic acid esters as taught by Dorigatti et

al. for the treatment of scarring on the skin by using the composition provided by Dorigatti et al. motivated by the teachings of Davidson et al. which teaches utilization of hyaluronate esters in wound healing and scarring treatment. Dorigatti also teaches utilization of non woven materials for medical applications because it provides fluid absorption, therefore one of ordinary would have been further motivated to utilize non woven material and benzyl ester of hyaluronic acid for wound treatment and ultimate scar reduction. Regarding claim 19, patent office is not equipped with laboratory to conduct experiments; since the prior art teaches the claimed components and claimed method of treating, one of ordinary would expect similar results. A skilled artisan would have been motivated to use derivatives of hyaluronic acid such as esters of hyaluronic acid in treating the scarring of the skin and treatment of wound with a reasonable expectation of success.

The references discussed above do not teach non-woven fabric for application. Dorigatti et al. teach application biodegradable, biocompatible and bioabsorbable non-woven fabric materials for use in surgery for regeneration of tissues, the fabric provides better absorption and can be better moulded for the surface to be covered and absorbs liquids such as solutions of disinfectants etc. the non woven fabric includes esters of hyaluronic acid, see abstract, column 2, lines 5-10 and 20-25.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use non woven fabric in the teachings of Davidson and Valentini for better absorption properties and flexibility motivated by the teachings of Della Valle et al.

The references discussed above do not disclose that 25% of carboxyl group of benzyl ester is free or salified. Since Dorigatti (WO) discloses 75% benzyl ester, it is apparent that rest of the carboxyl groups will be free.

To that end, DellaValle et al. teach process of hyaluronic acid esterification in which the extent of esterification can be varied and which shows that esterification can be from 25% to 75% and rest of the carboxyl groups are either free or salified, the reference also teaches salifiaction with inorganic salt, ,alkaline, potassium salt, see claims.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have salify the free carboxyl groups of hyaluronic acid ester because the process was known in the art. Utilization of known process of esterification would have resulted predictable results. Application of fabric to obtain optimum results for wound healing is optimizable parameter depending upon the extent of treatment required.

Response to Arguments

5. Applicant's arguments filed 09/24/10 have been fully considered but they are not persuasive.

Applicant argues that the Davidson reference refers to the ethyl ester of hyaluronic acid. (Davidson, page 172, col. 1, lines 10 and 43-44). Based on the Davidson reference itself, hyaluronic acid and hyaluronic acid 75% ethyl ester did not show any significant improvement in the progression of wound healing. (Davidson, page

174, col. i, lines 3-6 and 25-28, discussed in the Zanellato Declaration dated April 14, 2008, page 3). Furthermore, Applicants have presented evidence demonstrating that in a direct comparison, the ethyl ester had > 40% more scarring (scarred areas of treatment) thin1 treatment with a benzyl ester. (Zanellato Declaration, dated February 3, 2009, page 2, and point 8). More importantly, scarring was increased in animals treated with the ethyl ester of hyaluronic acid as compared to controls. (Zanellato Declaration, February 3, 2009, page 2). Thus, based on Davidson one of skill in the art would have no reasonable expectation that 1) hyaluronic acid (and its derivatives) would work better than controls at wound healing or reducing scarring, and 2) the benzyl ester of hyaluronic acid (as opposed to the ethyl ester) would be significantly better than either the ethyl ester *or* controls at improving wound healing and (Valentini, abstract). Based on Davidson, which tested both hyaluronic acid and the ethyl ester of hyaluronic acid, neither showed any improvement over treatment with the vehicle (alginate).

Regarding Valentini applicant argues that, simply because Valentini proposes the use of both the total benzyl ester of hyaluronic acid and the 75% benzyl ester of hyaluronic acid in a different form and for a different purpose would not lead one of skill in the art to expect that I) the benzyl ester would look for the reduction of scarring, o1" 2) the 75% benzyl ester would be significantly better than the total benzyl ester at the reduction of scarring than the total benzyl ester.

Applicant's arguments are not persuasive. Davidson teaches that the results show that ability of hyaluronate and its esterified derivatives stimulate early organization

of wound site while moderating the excessive accumulation of collagen at the stage of scar formation. (See page 174 columns 2, last paragraph). In response to applicant's assertion that the declaration shows more than 40 percent scarring treatment, it is pointed out that the declarations filed on 09/24/10 are insufficient to overcome the rejections. The declaration shows on page 2 in experimental design that the material applied to wound was on day zero with 75% benzyl ester of hyaluronic acid and application of 100 percent benzyl ester derivative was applied on seventh day after the surgery and not on day zero. This is not direct comparison, the significance of not comparing 100% benzylester applied at day zero versus 75% benzyl ester derivative applied at day zero is not clear to the examiner. In order to show that 75% benzyl ester derivative provides unexpected results versus 100% esterified derivative of hyaluronic acid, applicant is required to show direct comparison of application of the two derivatives at the same time interval. Since the declaration to show unexpected results is insufficient, the rejections made over combination of Davidson and Valentini will be maintained because as discussed above. Davidson teaches would healing and scarring with derivatives of hyaluronic acid and Valentini teaches 75% benzyl ester derivative of hyaluronic acid used for wound healing, tissue repair and tissue reconstruction which comprises a biologically active molecule, abstract.

6. DECLARATION SUBMITTED UNDER 37 CFR. § 1.132

Applicant's arguments that the attached are the results of the study conducted and from these results it can be seen that samples D and E according to the present invention exhibited an improvement of about 40% in the wound coverage versus all control samples.

The declaration is insufficient to overcome the rejections made in this office action.

The prior art discloses the scarring and wound healing effect by benzyl ester of hyaluronic acid. The increase in 40% of wound healing is a matter of degree and not an unexpected result where the prior art as discussed above specifically teaches application of hyaluronic acid benzyl derivatives in treating scars and wounds and utilization of non-woven fabric.

Applicants argue unexpected results by providing a Declaration from Dr. Callegaro which provides evidence showing the efficacy of a non-woven fabric of HYAFF 1tp75 *(i.e.,* the 75% benzyl ester) to the treatment with a laser skin autograph which is comprised of a 100% benzyl ester of hyaluronic acid, and a combination of treatment with both the 75% benzyl ester and the total benzyl ester of hyaluronic acid. In the Declaration, Dr. Callegaro indicates that the 75% benzyl ester of hyaluronic acid performs better than the total benzyl ester of hyaluronic acid. (Callegaro Declaration, page 3) In addition, the 75% benzyl ester provided "a better organized wound bed" and a strong angiogenic response *(i.e.,* directed angiogenesis). (Callegaro Declaration, page 4).[1] Also, Dr. Callegaro states that the addition of the 100% benzyl ester to the treatment with the 75% benzyl ester did not seem to significantly increase wound

healing. (Callegaro Declaration, page 4).

Applicant's arguments are not persuasive because the declaration shows on page 2 in experimental design that the material applied to wound was on day zero with 75% benzyl ester of hyaluronic acid and application of 100 percent benzyl ester derivative was applied on seventh day after the surgery and not on day zero. This is not direct comparison, the significance of not comparing 100% benzylester applied at day zero versus 75% benzyl ester derivative applied at day zero is not clear to the examiner. In order to show that 75% benzyl ester derivative provides unexpected results versus 100% esterified derivative of hyaluronic acid, applicant is required to show direct comparison of application of the two derivatives at the same time interval.

Applicant argues that Dr. Callegaro indicates that one of skill in the art would expect that the total benzyl ester would be the best material for tissue implant/repair and wound healing because Campoccia (Biomaterials 19 (1998) 210t-2127) indicates that the partial benzyl ester of hyaluronic acid (HYAFF 11p75) produces side effects regarding cell proliferation, adhesion and cell inflammation. (Callegaro Declaration, page 4). Thus, in his *opinion* as one of skil1 in the art, supported by the evidence in the Navsaria Report, a skilled practitioner would be led to use the total benzyl ester of hyaluronic acid, and therefore the benefits obtained with the 75% benzyl ester would be unexpected.

Applicants arguments are not persuasive because no substantial evidence have been provided in the form of experimental and technical data to support that utilization

of 100 percent benzyl ester derivative provides side effects. Applicant's opinion does not take place of substantial evidence to show unexpected results.

Applicants argue that the Examiner's reliance on the present application to provide the "reasonable expectation of success" based on the combined references is wholly improper, and smacks of hindsight reasoning. *See e.g., hi re Omeprazole Patent Litigation,* 82 U.S.P.Q.2d 1643, 1656 (Fed. Cir. 2007).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Regarding Dorigatti applicant argues that Furthermore, combining Davidson with Dorigatti, one of skill in the art would still tack the 75% benzyl ester of hyaluronic acid because Davidson teaches ethyl esters. Moreover, one of skill in the art would have no reasonable expectation of success that the 75% benzyl ester could be used to treat scarring, because Dorigatti mentions only that the non-woven tissues of the genera of hyaluronic acid derivatives *might* be used for dermatology (among other purposes), and Davidson does not teach the benzyl ester at all. (Dorigatti, page 3, line 22). Similarly, Dorigatti makes no distinction between the benzyl esters and the ethyl esters, and thus,

one of skill in the art would expect that the benzyl ester would have no effect on scarring, as shown with the ethyl esters of Davidson. Thus, not only would one of skill in the art have no reasonable expectation of success, but one of skill in the art would find the present invention's effectiveness to be unexpected, as described above.

Applicants arguments are not persuasive because Dorigatti teaches multilayer non woven material comprising a layer in contact with the skin comprising esters of hyaluronic acid; the material can be utilized in medical applications including surgery, see abstract and the hyaluronic esters used can be those described in EPA 0216453, USP 4,851,521, 4,965,353 and 5202431, used alone or in mixtures in varying amount percentages, see page 4, lines 27-29. The layer can also comprise collagen, polysaccharides in the form of gel, agar etc. (Reads on biological or pharmacological compound) the example 1 on page 7 discloses HYAFF 11 and non woven layer, the reference also teaches 75% benzyl ester. Therefore applicants assertion that benzyl ester is not taught by Dorigatti is not persuasive. Since the declaration is insufficient to overcome the rejections due to incomplete experimental evidence to show unexpected results, the rejections will be maintained. Davidson has been combined for treating wounds with hyaluronic esters, the references by Dorigatti teaches use of non woven fabric for better flexibility and Della Vella teaches various extent of esterification. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the

Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612